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LETTER TO THE EDITOR

Patients with Common Cold Coronaviruses Tested Negative for IgG Antibody to SARS-CoV-2

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The need for accurate antibody testing in patients following symptomatic or asymptomatic infections with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is well documented. How we best utilize the data obtained from these antibody studies is still a haunting question (1). There are now over 160 serologic kits on the market for the detection of antibodies to this virus (2). Most are not Emergency Use Authorization (EUA)/FDA approved, and due to the poor performance of some of these assays, the FDA has requested more stringent data (2). In any case, a validation study is necessary prior to reporting patient results. One early issue in the validation/evaluation of antibody tests for evidence of SARS-CoV-2 infection is the possibility of cross-reacting antibodies from the plasma of patients who had been infected with one or more of the common cold coronaviruses (coronavirus 229E, HKU1, NL63, and OC43). Antibody testing for SARS-CoV-2 in these patients could result in reduced specificity of the SARS-CoV-2 antibody assays due to false-positive results from cross-reacting antibodies (3). This is a problem for numerous reasons, especially in a low-prevalence population where there could be more false positives than true positives. It also ties in with issues outlined in the Infectious Diseases Society of America (IDSA) guidelines (4) and in a commentary in Lancet (5) on how to best utilize antibody test data, especially when there could be false-positive results, including cross-reacting antibodies to the four common cold coronaviruses.

In the course of performing a validation study, plasma from three distinct groups of patients was selected for immunoglobulin G (IgG) antibody testing. The validation samples were from patients with previous exposure to SARS-CoV-2, as determined by a positive PCR test (Xpert Xpress SARS-CoV-2; Cepheid, Sunnyvale, CA; or cobas SARS-CoV-2 assay; Roche Molecular Systems, Branchburg, NJ); those with negative SARS-CoV-2 PCR tests; and patients with previous non-SARS-CoV-2 respiratory infections. This last group included plasma from 20 patients who had positive viral respiratory panel PCRs (FilmArray respiratory panel 2; BioFire Diagnostics, LLC, Salt Lake City, UT) for one of the four common cold coronaviruses. The plasma from these 20 patients was collected more than 4 weeks after the positive PCR. This would allow enough time for the synthesis of IgG antibodies in these patients (Table 1).

Testing was performed on an Abbott Architect i2000SR (Abbott Park, IL) automated analyzer using the SARS-CoV-2 immunoglobulin G (IgG) assay. The assay is designed to

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TABLE 1 IgG antibody test results in patients with PCR-documented common cold coronavirus infections

Patient[a]	RP2[b] PCR result	RP2[b] date	Serum date[e]	SARS-CoV-2 IgG result[c]	SARS-CoV-2 PCR result[d]
1	CV OC43	1/28/2019[e]	4/21/2020	Negative	Negative
2	CV NL63	12/29/2019	4/22/2020	Negative	Negative
3	CV HKU1	1/2/2020	4/4/2020	Negative	Not tested
4	CV HKU1	1/11/2020	4/20/2020	Negative	Negative
5	CV HKU1	1/12/2020	4/22/2020	Negative	Not tested
6	CV NL63	2/7/2020	4/9/2020	Negative	Negative
7	CV HKU1	2/11/2020	4/21/2020	Negative	Not tested
8	CV 229E	2/18/2020	4/20/2020	Negative	Negative
9	CV NL63	3/2/2020	4/22/2020	Negative	Not tested
10	CV NL63	3/4/2020	4/22/2020	Negative	Not tested
11	CV NL63	3/4/2020	4/22/2020	Negative	Not tested
12	CV NL63	3/4/2020	5/1/2020	Negative	Not tested
13	CV NL63	3/5/2020	4/22/2020	Negative	Not tested
14	CV HKU1	3/6/2020	5/4/2020	Negative	Negative
15	CV NL63	3/6/2020	4/22/2020	Negative	Not tested
16	CV NL63	3/9/2020	4/21/2020	Negative	Negative
17	CV HKU1	3/9/2020	4/18/2020	Negative	Negative
18	CV HKU1	3/9/2020	4/30/2020	Negative	Not tested
19	CV OC43	3/11/2020	4/29/2020	Negative	Not tested
20	CV NL63	3/23/2020	4/22/2020	Negative	Negative

[a]Males (17) and females (3); age range, 28–88.
[b]Respiratory panel 2 film array; BioFire Diagnostics, LLC, Salt Lake City, UT.
[c]Abbott Architect SARS-CoV-2 IgG antibody test.
[d]Either Cepheid Xpert Express SARS-CoV-2 PCR or Roche cobas PCR assay (see text).
[e]All dates are mo-day-year.

detect IgG antibodies to the nucleocapsid protein of SARS-CoV-2. The antibody binds to SARS-CoV-2 antigen-coated microparticles and undergoes a chemiluminescent reaction, producing a direct relationship between the amount of IgG and relative light units. The presence of antibody is determined by comparing the relative light units in the reaction to the relative light units in the calibrator. The presence of antibody above the quantitative cutoff of 1.4 (index sample calibrator) is interpreted as positive.

All 20 patients tested negative for IgG antibody to SARS-CoV-2 (Table 1). Although the sample size was minimal, these data are reassuring that at least for the Abbott Architect SARS-CoV-2 antibody test, plasma from patients with documented positive PCRs for these four common cold coronaviruses did not test positive for the SARS-CoV-2 IgG antibody. This small study does not rule out that possibility. It does provide data that in our small study population, cross-reacting antibodies were not detected. Conclusions are limited by the small sample size of a predominantly elderly male population, consistent with the veteran population we studied. However, this multisite study, including data from 3 regional Veterans Affairs (VA) institutions (MA, CT, and VT) suggests that cross-reacting antibodies are not detected when testing for SARS-CoV-2 IgG antibody.

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